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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/621,760	07/17/2003	David L. Lewis	Mirus.030.09.2	9319
25032	7590	09/07/2007		
MIRUS CORPORATION 505 SOUTH ROSA RD MADISON, WI 53719			EXAMINER POPA, ILEANA	
			ART UNIT 1633	PAPER NUMBER
			MAIL DATE 09/07/2007	DELIVERY MODE PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/621,760	<b>Applicant(s)</b> LEWIS ET AL.	
	<b>Examiner</b> Ileana Popa	<b>Art Unit</b> 1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 02 July 2007.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 1-3 and 5-9 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-3 and 5-9 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)                                | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                       | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

### **DETAILED ACTION**

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in the prior Office action.

2. Claim 4 has been cancelled. Claim 1 has been amended.

Claims 1-3 and 5-9 are pending and under examination.

### ***Priority***

3. Applicant argues that the U.S. Patent 7,101,995 provides support for polyvinylamine in column 2, lines 21-25 combined with column 14, lines 25-45). It is noted that in column 2, lines 21-25, the specification discloses the use of siRNA for inhibiting gene expression. Column 14, lines 24-45 only discloses that polymers could be obtained using vinyl-containing monomers; the cited passage discloses that amines such as spermine or spermidine could be used, however, there is no disclosure of vinylamine. It is noted that the genus of vinyl-comprising monomers is large and in the absence of the specific disclosure of vinylamine as monomer, Applicant's argument that the '995 patent provides support for polyvinylamine is not found persuasive. Therefore, the priority date for the instant application is its filing date, i.e., 07/17/2003.

### ***Double Patenting***

4. Claims 1-3 and 5-9 remain rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 6, and 7 of U.S. Patent No. 5,744,335, in view of both Wolfert et al. (Bioconjugate Chem, 1999, 10: 993-100, of

record) and Leake et al. (PGPUB 2004/0224405) for the reasons of record set forth in the non-final Office action of 03/26/2007. Applicant's arguments filed 07/02/2007 have been fully considered but they are not persuasive.

Applicant traversed the instant rejection on the grounds that, while any polycation of sufficient size will condense plasmid DNA, not every polycation will function as a DNA transfection reagent. Applicant argues that a polymer that functions as a good transfection reagent with plasmid DNA will not necessarily function as a good transfection reagent with siRNA; Applicant cites Meyer et al. (Human Gene Therapy, 2006, 17: 1062-1076, p. 1071 column 1, third full paragraph) and the Declaration filed with the reply of 12/11/2006 to support this argument. Therefore, Applicant argues, it would not have been obvious to combine the polyvinylamine of Wolfert et al. with the lipid of the '335 patent to create a siRNA transfection delivery composition. For the reasons above, Applicant requests reconsideration of the rejection.

Applicant's arguments are acknowledged, however, the rejection is maintained for the following reasons:

While it is true that Meyer et al. teach that composition successful for delivery of plasmid DNA are not always suitable for siRNA delivery, this is in the context of carriers comprising lysine and histidine residues or high molecular weight PEI; there is no disclosure of polyvinylamine as being unsuitable for siRNA delivery. On the contrary, the prior art teaches that polyvinylamine or polyvinylamine in combination with a lipid (i.e., an amphipatic compound) can be used as a transfection agent to deliver siRNA to cells (see for example Gould-Fogerite et al., PGPUB 2005/0013855, p. 2, paragraph

0015, p. 17, paragraph 0188; Trubetskoy et al., PGPUB 2004/0162235, Abstract, p. 1, paragraph 0001, p. 2, paragraphs 0013-0015, p. 3, paragraph 0023, p. 5, paragraph 0060). Based on these teachings in the prior art, it would have been obvious to one of skill in the art to combine the polyvinylamine of Wolfert et al. with the lipid of '335 patent. One of skill in the art would have been motivated to do so because Wolfert et al. teach that polyvinylamine complexes are suitable for intranuclear delivery and because Wolff et al. teach their amphipatic compound as being able to enhance transfection efficiency (see also below).

The Declaration under 37 CFR 1.132 filed on 12/11/2006 is insufficient to overcome the rejection of claims 1-3 and 5-9 based upon the references above as set forth in the last Office action because the data presented do not pertain to the instant invention. The data presented in the Declaration describe the results obtained with a complex between the lipid of the '335 patent, polyvinylamine, and DNA (not siRNA as claimed). It is noted that the complex in the declaration mediates the delivery of a DNA encoding a gene to be expressed, wherein expression requires transcription and translation, whereas the instant complex delivers siRNAs for inhibition of gene expression, wherein siRNAs need only be present inside the cells for inhibition of gene expression (i.e., in the absence of transcription and translation). It is clear that these complexes are not structurally and functionally identical and therefore it is not proper to extrapolate the data in the Declaration to the complex taught by the references above.

For these reasons, the rejection is maintained.

5. The rejection of claims 1-3 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3 of U.S. Patent No. 7,101,995, in view of both Wolfert et al. and Leake et al. is withdrawn because Applicant submitted a terminal disclaimer on 07/02/2007.

6. The provisional rejection of claims 1-3 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3 of copending Application No. 10/845,968 is withdrawn because Applicant submitted a terminal disclaimer on 07/02/2007.

***Claim Rejections - 35 USC § 103***

7. Claims 1-3 and 5-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wolff et al. (U.S. Patent No. 5,744,335), in view of each Wolfert et al., Pollard et al. (J Biol Chem, 1998, 27: 7507-7511), and Leake et al., for the reasons of record set forth in the prior Office actions. Applicant's arguments filed 07/02/2007 have been fully considered but they are not persuasive.

Applicant traversed the instant rejection on the grounds that polyvinylamine cannot be reasonably anticipated to substitute for the histone of Wolff et al. to form an effective siRNA delivery composition. Applicant argues that there is no evidence of record to suggest that polyvinylamine together with the amphipathic compound of Wolff et al. will form a siRNA delivery agent. Applicant points out that he submitted evidence that, if polyvinylamine is substituted for the histone of Wolff et al., the resultant

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composition does not form a DNA delivery reagent. Applicant submits that ability of a polycation to condense nucleic acid does not prove that the polycation is a good transfection agent and, similarly, the ability of a polycation to be displaced from DNA following microinjection does not prove that the polycation is a transfection reagent. Applicant argues that the utility of a polymer to function as a transfection agent in combination with one set of compounds does not prove that the same polymer will function as a transfection agent with a second set of compounds. Applicant points out that the microinjection of Wolfert et al. is not transfection, and therefore, expression of a DNA following microinjection cannot reasonably predict transfection ability. Applicant also points out that Wolfert et al. teach that polyvinylamine gives no significant spontaneous transfection when applied to cells *in vitro* (p. 999, column 2, second paragraph). Applicant also asserts that the Examiner's statement that the prior art teaches the desirability to target siRNA to the nucleus is incorrect, as siRNA exerts its effects in cytoplasm and not in the nucleus (Meyer et al., p. 1063, column 1, second full paragraph). Applicant also argues that the data presented in the Declaration filed on 12/11/2006 directly address the obviousness of combining the polyvinylamine of Wolfert et al. with the amphipatic compound of Wolff et al. Applicants submits that the Declaration clearly shows that combining the two results in a composition that fails to deliver plasmid DNA to a cell (i.e., the functional test of Wolff et al.). Therefore, Applicant argues, one of skill in the art would not have been motivated to combine the teachings of Wolfert et al. and Wolff et al. and the further extrapolation of teachings of

Wolfert et al. to the delivery of siRNA cannot be considered obvious. For these reasons, Applicant requests reconsideration of the rejection.

Applicant's arguments are acknowledged, however, the rejection is maintained for the following reasons:

Applicant argues that there is no evidence of record to suggest that polyvinylamine together with the amphipathic compound of Wolff et al. will form a siRNA delivery agent. As noted above, the prior art does teach that 1,4 disubstituted piperazine in combination with any synthetic polycation (i.e., including polyvinylamine) forms an efficient siRNA transfection reagent (see U.S. Patent No. 7,101,995, column 4, lines 1-39). The arguments that Wolfert et al. teach that polyvinylamine by itself gives no spontaneous transfection is not found persuasive because the rejection is based on the combined teachings of Wolff et al. and Wolfert et al., wherein the combined teachings disclose a transfection reagent that comprises polyvinylamine and a 1,4 disubstituted piperazine (i.e., not polyvinylamine by itself). It is the use of 1,4 disubstituted piperazine that facilitates spontaneous transfection. Wolff et al. clearly teach that it is the combination of histones and 1,4 disubstituted piperazine that enables the efficient gene transfer into a variety of cells (p. 2, lines 7-14 and 41-67, column 5, lines 16-24); it is noted that the art teaches that histones by themselves are poor transfection agents (see Zaitsev et al., Gene Therapy, 1997, 4: 586-592, Abstract, p. 589, column 2 and Fig. 5). Therefore, it is clear from the teachings of the prior art that the addition of 1,4 disubstituted piperazine renders poor transfecting polycations efficient transfection agents. For the same reasons above, the argument and the

Declaration filed on 07/02/2007 that microinjection is not transfection, and therefore, expression of a DNA following microinjection is not predictive of a polymer transfection ability is not found persuasive because, again, it pertains to polyvinylamine alone; the cited art teaches that the composition comprising polyvinylamine and 1,4 disubstituted piperazine is an efficient transfection agent.

With respect to the argument that the Examiner was incorrect in asserting that the prior art teaches the desirability to target siRNA to the nucleus, it is noted that the art does teach RNA interference in the nucleus. As a matter of fact, the Examiner supported her assertion by providing Leake et al. for teaching the desirability to deliver siRNA to the nucleus to inhibit non-coding nucleic acid sequences, such as promoters or enhancers. (p. 1, paragraphs 0005, 0006, and 0012-0015, p. 2, paragraphs 0023-0029, p. 4, paragraph 0061, p. 4, paragraph 0062). It is not clear why Applicant chose not to mention this reference. It is noted that the art provides numerous references teaching RNA interference in the nucleus, for example Dudley et al. (Curr Opin Mol Ther, April 2003, 5: 113-117, Abstract, p. 114, columns 1 and 2, p. 115, columns 1 and 2), Mette et al. (EMBO J, 2000, 19: 5194-5201, Abstract, p. 5198, column 2, last paragraph bridging p. 5199, p. 5199, column 1, second full paragraph), Vermaak et al. (Curr Opin Cell Biol, June 2003, 15: 266-274, p. 266, column 2, p. 267, column 1, first full paragraph), Morris et al. (Science, 2004, 305: 1289-1292, Abstract, p. 1291, column 3, first and second full paragraphs), to cite only a few. Therefore, the art teaches that siRNA can function both in the cytoplasm and the nucleus and Applicant's argument is not found persuasive.

With respect to the Declaration filed on 12/11/2006, it is noted that Applicant provided an additional Declaration under 35 C.F.R 1.132 stating that the lipid compound described in the 12/11/2006 Declaration is identical to the compound of Wolff et al. However, it is noted that the transfection complexes are not identical, since the complexes used in the Declaration comprise plasmid DNA, whereas the complexes taught by the combined references above (which are identical to the instant complexes) comprise siRNA and not plasmid DNA. To be convincing, Applicant should provide data demonstrating that a transfection reagent comprising polyvinylamine and 1,4 disubstituted piperazine cannot mediate the delivery of siRNA to the cells. In this case, it is noted that Applicant would provide evidence that his invention does not work. Is this what Applicant intends to say?

For the motivation to extrapolate the combined teachings of Wolfert et al. and Wolff et al. to the delivery of siRNA, see the Office action of 03/26/2007.

For all the reasons above, the rejection is maintained.

8. The rejection of claims 1-3 and 5-9 under 35 U.S.C. 103(a) as being obvious over Lewis et al. (U.S. patent No. 7,101,995), in view of each Wofert et al., Pollard et al., and Leake et al. is withdrawn because Applicant submitted a Declaration under 35 C.F.R 1.132 stating that the transfection reagent comprising polyvinylamine, amphipatic compound and siRNA disclosed by Lewis et al. was derived from the inventor of the instant application and it is not an invention by another. The Declaration was filed on 07/02/2007.

***Conclusion***

9. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure: Zaitsev et al., Gene Therapy, 1997, 4: 586-592; Dudley et al., Curr Opin Mol Ther, April 2003, 5: 113-117; Mette et al., EMBO J, 2000, 19: 5194-5201; Vermaak et al., Curr Opin Cell Biol, June 2003, 15: 266-274; Morris et al., Science, 2004, 305: 1289-1292. The art was cited in response to Applicant's arguments that there is no suggestion in the art to motivate one of skill in the art to combine polyvinylamine with 1,4 disubstituted piperazine or that the art does not teach intranuclear RNA interference.

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ileana Popa whose telephone number is 571-272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Ileana Popa, PhD

/Joseph Woitach/

Joseph Woitach

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